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Tumor Necrosis Factor Family

TUMOR NECROSIS FACTOR FAMILY

First printed in R&D Systems' 1998 Catalog.

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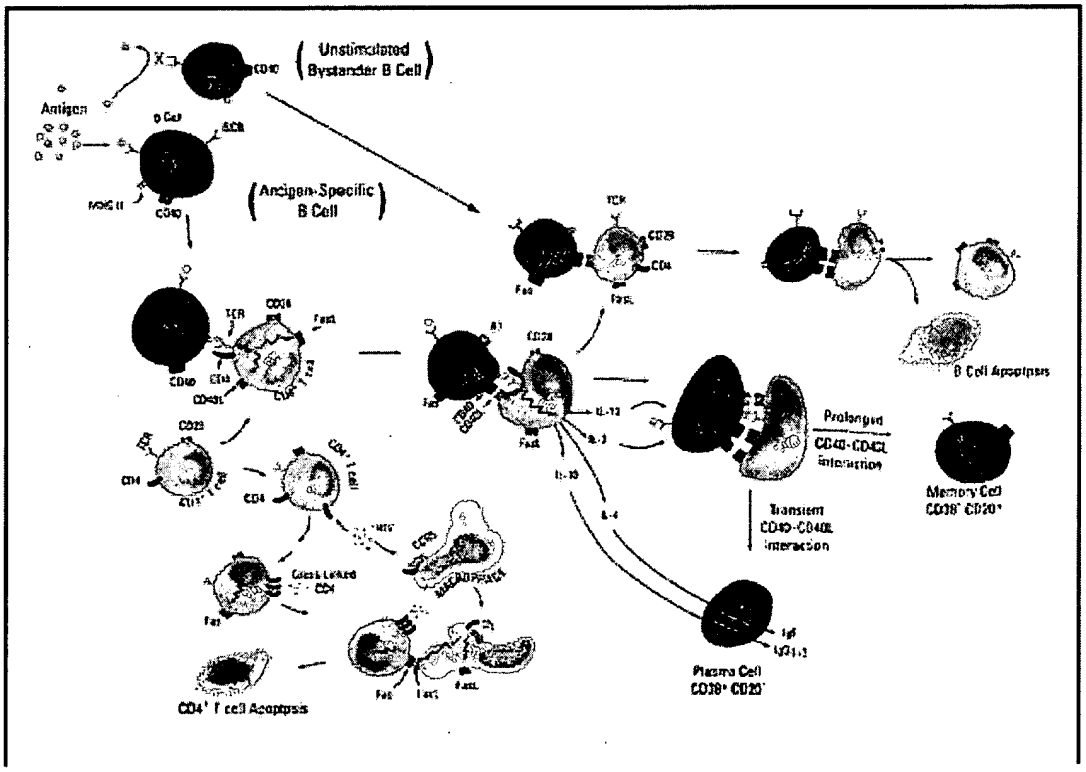

Fig. 1. TNF Superfamily involving Fas/FasL and CD40/CD40L.

Overview

The first suggestion that a tumor necrotizing molecule existed was made when it was observed that cancer patients occasionally showed spontaneous regression of their tumors following bacterial infections.[1] Subsequent studies in the 1960s indicated that host-associated (or endogenous) mediators, manufactured in response to bacterial products, were likely responsible for the observed effects.[2, 3] In 1975 it was shown that a bacterially-induced circulating factor had strong anti-tumor activity against tumors implanted in the skin in mice.[2, 4] This factor, designated tumor necrosis factor (TNF), was subsequently isolated,[5] cloned,[6] and found to be the prototype of a family of molecules that are involved with immune regulation and inflammation.[2, 7, 8] The receptors for TNF and the other members of the TNF superfamily also constitute a superfamily of related proteins.[9-12] Since a number of reviews have been published on the TNF superfamily (TNFSF) and the TNF receptor superfamily (TNFRSF),[2, 7-13] this review is designed only to provide simple, basic background information on all of the currently known receptors and ligands in this superfamily.

Ligands/Co-Receptors

TNF-related ligands usually share a number of common features. These features do not include a high degree of overall amino acid (aa) sequence homology.[7, 9] With the exception of nerve growth factor (NGF) and TNF-beta, all ligands are synthesized as type II transmembrane proteins (extracellular C-terminus) that contain a short cytoplasmic segment (10-80 aa residues) and a relatively long extracellular region (140-215 aa residues).[7] NGF, which is structurally unrelated to TNF, is included in this superfamily only because of its ability to bind to the TNFRSF low affinity NGF receptor (LNGFR). NGF has a classic signal sequence peptide and is secreted. TNF-beta, in contrast, although also fully secreted, has a primary structure much more related to type II transmembrane proteins. TNF-beta might be considered as a type II protein with a non-functional, or inefficient, transmembrane segment.[7, 8] In general, TNFSF members form trimeric structures, and their monomers are composed of beta-strands that orient themselves into a two sheet structure.[8, 10, 11] As a consequence of the trimeric structure of these molecules, it is suggested that the ligands and receptors of the TNSF and TNFRSF superfamilies undergo "clustering" during signal transduction.[11, 13]

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NGF:

Human NGF is a 12.5 kDa, nonglycosylated polypeptide 120 aa residues long.[14, 15] Synthesized as a prepropeptide, there is an 18 aa residue signal sequence, a 103 aa residue N-terminal pro-sequence, and a 120 aa residue mature segment. Human to mouse, there is 90% aa sequence identity in the mature segment. In the mouse, NGF is referred to as beta-NGF, due to the existence of NGF in a 130 kDa (7S) heterotrimeric (aß?) complex in submaxillary glands.[15, 16] Many cells, however, do not synthesize all the components of this 7S complex, and the typical form for NGF is a 25 kDa, non-disulfide linked homodimer.[14, 16] NGF and all other neurotrophins bind to the LNGFR, a member of the TNFRSF.[17]

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CD40L:

Human CD40L is a 39 kDa, type II (extracellular C-terminus) transmembrane glycoprotein that was originally identified on the surface of $CD4^+$ T cells.[18] With a predicted molecular weight of 29 kDa, CD40L is 261 aa residues long, with a 22 aa residue cytoplasmic domain, a 24 aa residue transmembrane segment, and a 215 aa residue extracellular region.[18] Human to mouse, CD40L is 73% identical at the aa sequence level and mouse CD40L is apparently active in humans.[19] Although usually considered to be a membrane bound protein, natural, proteolytically cleaved 15-18 kDa soluble forms of CD40L with full biological activity have also been described.[20, 21] Like TNF-alpha, CD40L is reported to form natural trimeric structures.[20, 22] Cells known to express CD40L include B cells, $CD4^+$ and $CD8^+$ T cells,[23] mast cells and basophils,[24] eosinophils,[25] dendritic cells,[26] and monocytes, NK cells, and gd T cells.[27]

CD137L/4-1BBL:

Mouse 4-1BBL is a 50 kDa, 309 aa residue transmembrane glycoprotein that is the largest of the TNFSF members.[28] With a predicted molecular weight of 34 kDa, the molecule has an 82 aa residue cytoplasmic

region, a 21 aa residue transmembrane segment, and a 206 aa residue extracellular domain. Although human and mouse 4-1BB molecules exhibit 60% identity at the aa level, human and mouse 4-1BBL molecules exhibit only 36% identity at the aa level. This level of cross species conservation is much lower than that shown by other members of the TNFSF.[11, 29] In mice, two ligands are known for 4-1BB: 4-1BBL and laminin.[30] Cells known to express 4-1BBL include B cells, dendritic cells, and macrophages.[31, 32]

TNF-alpha

:

Human TNF-alpha is a 233 aa residue, nonglycosylated polypeptide that exists as either a transmembrane or soluble protein.[6, 33, 34] When expressed as a 26 kDa membrane bound protein, TNF-alpha consists of a 29 aa residue cytoplasmic domain, a 28 aa residue transmembrane segment, and a 176 aa residue extracellular region.[7, 33] The soluble protein is created by a proteolytic cleavage event via an 85 kDa TNF-alpha converting enzyme (TACE),[35, 36] which generates a 17 kDa, 157 aa residue molecule that normally circulates as a homotrimer.[6, 37, 38] Normal levels of circulating TNF are reported to be in the 10-80 pg/mL range.[39, 40] While both membrane-bound and soluble TNF-alpha are biologically active, soluble TNF-alpha is reported to be more potent.[41] Mouse to human, full-length TNF-alpha shows 79% aa sequence identity.[42, 43] Unlike human TNF-alpha, mouse TNF-alpha is glycosylated.[42, 43] The variety of cell types known to express TNF-alpha is enormous and includes macrophages, $CD4^+$ and $CD8^+$ T cells,[44] adipocytes,[45] keratinocytes,[46] mammary and colon epithelium,[47, 48] osteoblasts,[49] mast cells,[50] dendritic cells,[51] pancreatic beta-cells,[52] astrocytes,[53] neurons,[54] monocytes,[55] and steroid-producing cells of the adrenal zona reticularis.[56]

CD134L/OX40L:

OX40, the receptor for OX40L, is a T cell activation marker with limited expression that seems to promote the survival (and perhaps prolong the immune response) of $CD4^+$ T cells at sites of inflammation.[57] OX40L also shows limited expression. Currently only activated $CD4^+$, $CD8^+$ T cells,[58] B cells,[59, 60] and vascular endothelial cells have been reported to express this factor.[61] The human ligand is a 32 kDa, 183 aa residue glycosylated polypeptide that consists of a 21 aa residue cytoplasmic domain, a 23 aa residue transmembrane segment, and a 139 aa residue extracellular region.[7, 57] When compared to the extracellular region of TNF-alpha, OX40L has only 15% aa sequence identity, again emphasizing the importance of secondary and tertiary structures as the basis for inclusion in the TNF Superfamily.[57] Human OX40L is 46% identical to mouse OX40L at the aa sequence level. Mouse OX40L is active in humans, but human OX40L is inactive in mice.[58] Consistent with other TNFSF members, OX40L is reported to exist as a trimer.[62]

CD27L/CD70:

Human CD27L is a 50 kDa, 193 aa residue type II (extracellular C-terminus) transmembrane glycoprotein that appears to have a very limited immune system expression pattern.[63, 64] Having less than 25% aa sequence identity to TNF-alpha and CD40L, the molecule has only a 20 aa residue cytoplasmic segment, an 18 aa residue transmembrane domain, and a 155 aa residue extracellular region.[64] Although the 20 aa residue cytoplasmic segment is short by most standards, there is a suggestion that it has a signaling function, perhaps activating the cytolytic program of gd T cells[65] and/or contributing necessary signals for antibody production in B cells.[66] Cells known to express CD27L are usually activated cells and include NK cells,[67] B cells,[66] $CD45RO^+$, $CD4^+$ and $CD8^+$ T cells,[68] gd T cells,[65] and certain types of leukemic B cells.[69]

FasL:

Fas ligand (FasL) is a highly conserved, 40 kDa transmembrane glycoprotein that occurs as either a membrane bound protein or a circulating homotrimer.[70, 71] In humans, FasL is synthesized as a 281 aa residue protein with an 80 aa residue cytoplasmic region, a 22 aa residue transmembrane segment, and a 179 aa residue extracellular domain.[70] When proteolytically cleaved, FasL is a 70 kDa homotrimer composed of 26 kDa monomers with full biological activity.[71] In mice, the FasL is somewhat different. Although mouse FasL molecule has 77% aa sequence identity with human FasL,[70, 72, 73] polymorphisms exist in the mouse FasL, leading to functionally distinct FasL forms.[74] In addition, a one aa residue substitution at position 273 (Phe to Leu) results in the *gld/gld* (generalized lymphoproliferative disease) mutation.[72] Finally, while FasL in a membrane-bound form shows species cross-reactivity,[70] soluble mouse FasL is apparently biologically inactive.[71] Cells known to express FasL include type II pneumocytes

and bronchial epithelium,[75] monocytes,[76] LAK cells and NK cells,[77, 78] dendritic cells,[79] B cells,[80] macrophages,[81] $CD4^+$ and $CD8^+$ T cells,[82] and colon and lung carcinoma cells.[75, 83]

CD30L:

Human CD30L is a 40 kDa, 234 aa residue transmembrane glycoprotein with 72% aa sequence identity to its mouse counterpart.[84] With a predicted molecular weight of 26 kDa, the molecule consists of a 46 aa residue cytoplasmic region, a 21 aa residue transmembrane segment, and a 172 aa residue extracellular domain.[84] Species cross-reactivity has been reported.[84] As suggested for CD27L, the cytoplasmic region is suggested to transduce a signal.[85] The CD30/CD30L system is complex since CD30 ligation can induce both proliferation and apoptosis.[84] Cells known to express CD30L include monocytes and macrophages,[84] B cells plus activated $CD4^+$ and $CD8^+$ T cells,[86] neutrophils, megakaryocytes, resting $CD2^+$ T cells, erythroid precursors,[87] and eosinophils.[88]

TNF-beta/LT-alpha

:

TNF-beta, otherwise known as lymphotoxin-alpha (LT-alpha) is a molecule whose cloning was contemporary with that of TNF-alpha.[89] Although TNF-beta circulates as a 171 aa residue, 25 kDa glycosylated polypeptide, a larger form has been found that is 194 aa residues long.[90] The human TNF-beta cDNA codes for an open reading frame of 205 aa residues (202 in the mouse),[89, 91] and presumably some type of proteolytic processing occurs during secretion. As with TNF-alpha, circulating TNF-beta exists as a non-covalently linked trimer and is known to bind to the same receptors as TNF-alpha.[92-95] Circulating TNF-beta levels are reported to be about 150 pg/mL.[96] Human TNF-beta is 72% identical to mouse TNF-beta at the aa sequence level across the entire molecule.[91] TNF-alpha to TNF-beta, aa sequence identity is reported to be 28%.[6, 93] Unlike TNF-alpha, TNF-beta does not have a transmembrane form. However, it can be membrane-associated, due to its binding to membrane-anchored LT-beta (see below).[92, 97] In this complex, TNF-beta and LT-beta will form a heterotrimer that binds to both the LT-beta receptor and TNFRI receptor. Activation of the TNFRI receptor, however, does not occur.[92, 94] Cells known to express TNF-beta include NK cells, T cells and B cells.[97]

LT-beta:

Human lymphotoxin-beta (LT-beta), also known as p33, is a 33 kDa type II (extracellular C-terminus) transmembrane glycoprotein originally cloned from a T cell hybridoma cell line. It is 244 aa residues long, and has a 16 aa residue cytoplasmic segment, a 31 aa residue transmembrane domain, and a 197 aa residue extracellular region.[7, 98] On the membrane surface, LT-beta readily forms a trimeric complex with TNF-beta, in either a 2:1 (major form) or a 1:2 (minor form) ratio.[92, 98] LT-beta is not secreted.[94] A comparison of human to mouse LT-beta shows 80% aa sequence identity in homologous regions.[99] Overall, however, the mouse gene shows significant differences from the human gene. In mice, an intron has been incorporated into the genome creating a 66 aa residue insert into what would otherwise be a 240 aa residue molecule.[100]

TRAIL:

TRAIL, or TNF-related apoptosis-inducing ligand, is a newly discovered TNFSF member initially cloned from human heart and lymphocyte cDNA libraries.[101] With a predicted molecular weight of 32 kDa, human TRAIL is 281 aa residues long, with a 17 aa residue cytoplasmic tail, a 21 aa residue transmembrane segment, and 243 aa residue extracellular region.[101, 102] Human TRAIL is 65% identical to mouse TRAIL at the aa sequence level across the entire molecule and there is complete species cross-reactivity.[101] As a membrane bound protein, TRAIL shows a trimeric structure.[102] Although TRAIL is known to be expressed by lymphocytes, many tissues seem to express the ligand, and this broad expression pattern suggests an intriguing function for the molecule.[101]

Receptors

As with members of the TNF Superfamily, members of the TNF Receptor Superfamily (TNFRSF) also share a number of common features. In particular, molecules in the TNFRSF are all type I (N-terminus extracellular) transmembrane glycoproteins that contain one to six ligand-binding, 40 aa residue cysteine-rich motifs in their extracellular domain.[7, 9-11] In addition, functional TNFRSF members are usually trimeric or multimeric complexes that are stabilized by intracysteine disulfide bonds. Unlike most

members of the TNFSF, TNFRSF members exist in both membrane-bound and soluble forms.[9] Finally, although aa sequence homology in the cytoplasmic domains of the superfamily members does not exceed 25%,[7] a number of receptors are able to transduce apoptotic signals in a variety of cells, suggesting a common function.[9, 103]

LNGFR/p75:

The human low-affinity nerve growth factor receptor (LNGFR) is a 75 kDa, 427 aa residue type I (extracellular N-terminus) transmembrane glycoprotein. The 427 aa residue receptor contains a 25 aa residue signal sequence, a 225 extracellular region, a 23 aa residue transmembrane segment, and a 154 aa residue cytoplasmic domain.[7, 104, 105] There are four cysteine-rich domains in its extracellular region. A comparison of human to rat LNGFR shows 92% aa sequence identity in the extracellular domain, and 95% aa sequence identity in the cytoplasmic region.[104, 106] In its functional form, it often appears as an approximately 200 kDa disulfide-linked homodimer.[104, 105] All neurotrophins bind to LNGFR with the same K_d of approximately 1-3 nM.[17, 105, 106] In contrast to the high-affinity neurotrophin receptors (Trks), LNGFR has no inherent tyrosine kinase activity.[107] It has been suggested that LNGFR passes NGF to the physiologically-active Trks.[108, 109] However, recent evidence now suggests that co-expressed LNGFR and TrkA modulate each others activities[110, 111] and that LNGFR signals on its own, utilizing a functional "death domain" in its cytoplasmic region.[112, 113] Soluble forms of 35- 45 kDa LNGFR are known to occur, presumably the result of proteolytic cleavage.[114] Cells known to express LNGFR include oligodendrocytes,[113] B cells (but not monocytes or T cells),[115] bone marrow fibroblasts,[116] autonomic and sensory neurons,[110, 117] Schwann cells,[117] follicular dendritic cells,[118] select astrocytes,[119] and mesenchymal cells involved with mesenchymal-epithelial interactions.[120]

CD40:

CD40 is a 50 kDa, 277 aa residue transmembrane glycoprotein most often associated with B cell proliferation and differentiation.[121, 122] Expressed on a variety of cell types, human CD40 cDNA encodes a 20 aa residue signal sequence, a 173 aa residue extracellular region, a 22 aa residue transmembrane segment, and a 62 aa residue cytoplasmic domain.[122] There are four cysteine-rich motifs in the extracellular region that are accompanied by a juxtamembrane sequence rich in serines and threonines. Mouse CD40 is 62% identical to human CD40 at the aa sequence level. However, mouse CD40 is 305 aa residues long with the difference attributable to a 28 aa residue extension in the cytoplasmic tail.[123] CD40 ligation is associated with the induction of apoptosis. This is not due the activation of a cytoplasmic "death domain"; rather CD40 ligation can upregulate Fas antigen, which primes cells for subsequent Fas-mediated apoptosis.[124] Currently, it is believed that the normal signaling pathway of CD40 involves both NF-kB, and protein kinase (*lyn*) activation.[125] Soluble CD40 has been identified in B cell cultures, presumably the result of proteolytic processing.[126, 127] Although many functions have been attributed to CD40, one suggests that CD40 ligation preferentially drives B cells into memory cells rather than plasma cells.[128] Cells known to express CD40 include B cells.[123] monocytes and basophils (but not mast cells),[129] eosinophils,[130] endothelial cells,[131] interdigitating dendritic cells,[132] Langerhans cells,[133] blood dendritic cells,[134] fibroblasts,[135] keratinocytes,[136] Reed-Sternberg cells of Hodgkin's disease, and Kaposi's sarcoma cells.[137, 138] A review on CD40 can be found in reference 121.

CD137/4-1BB/ILA:

Human CD137 is a 30-35 kDa activation-induced glycoprotein that occurs as both a monomer and homodimer on the surface of cells.[7, 139-141] CD137 is aa residues long, including a 17 aa residue signal sequence, a 169 aa residue extracellular region, a 27 aa residue transmembrane segment, and a 42 aa residue cytoplasmic domain.[29, 139, 142] In the extracellular region, CD137 contains the characteristic multiple cysteine-rich motif.[7] Mouse to human, although there is 60% aa sequence identity across the open reading frame,[29, 143] there is minimal to no cross-species biological activity.[29, 144] The K_d for CD137L binding to CD137 is reported to be about 30 pM.[29] Soluble CD137 is known to exist, but unlike the soluble forms of TNFRI & II, CD40 and LNGFR, it is created by an alternative splicing event.[145] CD137 ligation is reported to interrupt T cell apoptotic programs associated with activation-induced cell death.[146] Cells known to express CD137/4-1BB/ILA (for induced by lymphocyte activation) include fibroblasts,[145] thymocytes,[145] monocytes,[139, 145] and $CD4^+$ and $CD8^+$ T cells.[141]

TNFRI/p55/CD120a:

TNFRI is a 55 kDa, 455 aa residue transmembrane glycoprotein that is apparently expressed by virtually

all nucleated mammalian cells.[147-149] The molecule has a 190 aa residue extracellular region, a 25 aa residue transmembrane segment, and a 220 aa residue cytoplasmic domain.[7, 147] In a comparison of mouse to human proteins, TNFRI has 64% aa sequence identity (70% in the extracellular region), with mouse and human TNFRI binding human and mouse TNF-alpha with equal affinity.[150, 151] The extracellular region has four cysteine-rich motifs, the first of which is suggested to be required for binding.[152] The cytoplasmic domain has an 80 aa residue "death domain" that can trigger an apoptotic pathway.[153] This is not the only outcome of TNFRI ligation, however. NF-kB is also activated by the TNFRI, although the mechanism determining the choice of pathways is not clear.[154] Both TNF-alpha and TNF-beta bind to TNFRI. Soluble TNF-alpha binds with a K_d in the range of 20-60 pM,[152, 154] while TNF-beta binds with a K_d equal to 650 pM.[152] While TNFRI relative to TNFRII has been suggested to be the more physiologically-relevant receptor, recent evidence suggests that TNFRI is most important for circulating TNF-alpha, while membrane-bound TNF-alpha associates with TNFRII[154] (see TNFRII below). Soluble TNFRI, which blocks TNF-alpha activity, has been identified in both urine and blood (1-3 ng/mL).[39, 40, 155] Soluble forms of at least two molecular weights (32 kDa and 48 kDa) have been identified and are believed to be generated by proteolytic cleavage.[149, 156, 157] Among the numerous cells known to express TNFRI are hepatocytes,[40] monocytes and neutrophils,[158] cardiac muscle cells,[159] endothelial cells,[160] and $CD34^+$ hematopoietic progenitors.[161]

TNFRII/p75/CD120b:

Human TNFRII is a 75 kDa, 461 aa residue transmembrane glycoprotein originally isolated from a human lung fibroblast library.[162] This receptor consists of a 240 aa residue extracellular region, a 27 aa residue transmembrane segment and a 173 aa residue cytoplasmic domain.[7, 162] Mouse to human, aa sequence identity in TNFRII cytoplasmic domain is 73 %, while aa sequence identity in the extracellular region falls to 58%.[150] This drop in extracellular identity is reflected in the observation that human TNF-alpha is not active in the mouse system.[150] TNFRII to TNFRI, aa sequence identity is only about 20% in the extracellular region and 5% in the cytoplasmic domain.[150] The function of TNFRII is not clear. In the TNF-alpha system, it has been suggested that TNFRII binds TNF-alpha and transfers it to TNFRI, which then is activated and initiates a physiological response.[163, 164] TNF-alpha binding to TNFRII clearly has an effect on cells, however, inducing apoptosis in rhabdomyosarcoma (skeletal muscle tumor) cells,[165] and cell migration in Langerhans cells.[166] A clue to understanding of TNFRII activity may lie in its binding kinetics. At 37 °C, soluble TNF-alpha binds to TNFRI with a K_d of 20 pM, and to TNFRII with a K_d of 300 pM (note: at 4 °C the K_d's are approximately equal at 100 and 300 pM respectively). Since TNF-alpha levels (at least systemically) are usually in the range of 100 pM, TNF-alpha activity will normally be mediated by the TNFRI molecule. In addition, a TNF-alpha:TNFRII interaction leads to a very slow oligomerization of receptor molecules, and ligand dissociation seems to occur before receptor-signaling complex formation. Thus, TNFRII could be envisioned to "hand-off" to TNFRI. However, not all TNF-alpha is soluble, and current theory predicts that membrane-bound TNF-alpha is the effective ligand for TNFRII. In this form, a TNF-alpha:TNFRII complex allows time for the slow formation of signal-transducting oligomers.[154] For TNF-beta, the K_d for TNFRII binding is reported to be approximately 300 pM. However, it would appear that a TNF-beta:TNFRII complex is non-signaling, leading to the suggestion that in the TNF-beta system, TNFRII is nothing more that a "decoy-receptor".[167] Soluble forms of TNFRII have been identified, resulting apparently from proteolytic cleavage by a metalloproteinase termed TRRE (TNF-Receptor Releasing Enzyme).[168, 169] The shedding process appears to be independent of that for soluble TNFRI.[170] Among the multitude of cells known to express TNFRII are monocytes,[170] endothelial cells,[171] Langerhans cells,[166] and macrophages.[172]

CD134/OX40/ACT35:

Human OX40 is a 48 kDa, type I (external N-terminus) transmembrane glycoprotein that appears to have a very limited pattern of expression,[173, 174] currently consisting of only activated $CD4^+$ and $CD8^+$ T cells.[174] The mature molecule is a 250 aa residue polypeptide that consists of a 188 aa residue extracellular region, a 26 aa residue transmembrane segment, and a 36 aa residue cytoplasmic domain.[7, 173] In the extracellular region, there is about 60% aa sequence identity human to mouse.[173, 175] There is marked species cross-reactivity in this system.[58, 174]

CD27:

Immune system cells are currently the only reported source for expression of CD27, a 50-55 kDa variably glycosylated polypeptide.[176, 177] The mature molecule has a predicted molecular weight of 27 kDa and is 242 aa residues long, consisting of a 175 aa residue extracellular region, a 21 aa residue transmembrane segment, and a 46 aa residue cytoplasmic domain.[7, 176] Mouse to human, CD27 is 65% identical at the aa

sequence level, with both molecules expressed as homodimers on the cell surface.[176, 178] Although CD27 lacks a recognizable cytoplasmic "death-domain" motif, it can induce apoptosis through a receptor-associated, death-domain containing a cytoplasmic protein known as Siva (the Hindu god of destruction).[179] Whether there are a number of such proteins specific for various TNFRSF members remains to be seen. A soluble, 32 kDa form of CD27 has been identified in both blood and urine, most likely the result of proteolytic processing.[177, 180] Cells known to express CD27 include NK cells,[181] B cells,[182, 183] $CD4^+$, $CD8^+$ T cells and thymocytes.[176]

Fas/CD95/APO-1:

Human Fas (fibroblast associated) is a 43 kDa, 355 aa residue transmembrane glycoprotein found on multiple cell types.[184] Also known as APO-1 (for Apoptosis-1), the molecule appears to be more than a simple mediator of apoptosis. On fibroblasts, Fas ligation can lead to either proliferation or apoptosis depending on the relative number of expressed Fas molecules.[185] The human receptor is 335 aa residues long, with a 156 aa residue extracellular region, a 20 aa residue transmembrane segment, and a 144 aa residue cytoplasmic domain.[7, 184] In the extracellular region, there are three cysteine-rich motifs, while in the cytoplasmic region there is a 68 aa residue "death-domain", which is also found in (and 25% identical to) the TNFRI cytoplasmic region.[153, 186] It is currently suggested that cytoplasmic death-domain containing proteins associate with this area (FADD protein with Fas, TRADD protein with TNFRI), thereby transmitting apoptotic signals.[187] Both FADD and TRADD are also known to associate with each other, suggesting considerable interaction between the apoptotic programs of each system.[187] There is 50% aa sequence identity in Fas molecules, mouse to human, with mouse Fas being eight aa residues shorter in length.[188] Soluble forms of Fas are known, the result of alternative gene splicing.[189, 190] In blood, soluble Fas is reported to circulate as a dimer and trimer at low ng/mL concentrations.[190] Cells reported to express Fas include $CD34^+$ stem cells,[161] fibroblasts,[185] NK cells,[191] keratinocytes,[92] hepatocytes,[193] B cells and B cell precursors,[194] monocytes plus $CD4^+$ and $CD8^+$ T cells,[195] $CD45RO^+$?d T cells,[196] eosinophils,[197] and thymocytes, with low levels detected on $CD4^-CD8^-$ precursors, and high levels on $CD4^+CD8^+$ precursors.[198] A review on Fas can be found in reference #199.

CD30/Ki-1:

Human CD30 is a 105-120 kDa transmembrane glycoprotein often associated with the Reed-Sternberg cells of Hodgkin's disease.[200, 201] Although in most cases, mouse to human, members of the TNFRSF are close in terms of overall length, CD30 shows a marked departure from the norm. Mature human CD30 is 577 aa residues long, with an 18 aa residue signal sequence, a 365 aa residue extracellular region, a 24 aa residue transmembrane segment, and a 188 aa residue cytoplasmic domain.[200] There are six cysteine-rich motifs in the extracellular region. In mice, mature CD30 is 480 aa residues long, with a 90 aa residue deletion in the extracellular region relative to the human.[202] This 90 aa residue differential eliminates three of the six cysteine-rich motifs found in humans.[202] Overall, there is approximately 60% aa sequence identity, mouse to human.[202] An 85 kDa form of soluble CD30 has been detected in the blood of patients with $CD30^+$ lymphomas.[203] Cells known to express CD30 include Reed-Sternberg cells,[201] $CD8^+$ T cells,[202] and $CD4^+$ T cells.[204] Of note, $CD30^+$ $CD4^+$ T cells are considered to be major producers of T cell-derived IL-5.[204]

LT-beta R:

Human LT-beta R (lymphotoxin-beta receptor) is a 75 kDa transmembrane glycoprotein that consists of a 201 aa residue extracellular region, a 26 aa residue transmembrane segment, and a 187 aa residue cytoplasmic domain.[7, 205, 206] In the extracellular region, it contains four cysteine-rich motifs. A comparison of mouse to human receptors shows 76% identity at the aa sequence level.[206] In terms of ligands, LT-beta R preferentially binds $(TNF\text{-}beta)_1(LT\text{-}beta)_2$ heterotrimers over LT-beta homotrimers. Mouse ligands are active on human receptors while human ligands are only marginally active on mouse receptors.[206] Relative to the TNFR receptors, LT-beta R is most like TNFRI in the first two cysteine-rich motifs, and most like TNFRII in the third and fourth cysteine-rich motifs.[206] LT-beta R is known both to activate NF-?B and to induce cell death via TRAF-3, making it somewhat analogous to TNFRI.[207] Genes known to be activated by LT-beta R include IL-8 and RANTES.[208] Based on cell lines, LT-beta R is found on monocytes, fibroblasts, smooth muscle and skeletal muscle cells.[208]

DR3/WSL-1/TRAMP/APO-3/LARD:

DR3 (or Death Receptor 3) is a 54 kDa, 417 aa residue type I (external N-terminus) transmembrane glycoprotein that has been isolated under a variety of names.[209] The DR3 designation results from this

being the third factor discovered with an intracellular "death domain", TNFRI being the first and Fas being the second.[209] Also known as APO-3,[210] Wsl-1,[211] LARD (lymphocyte-associated receptor of death),[212] and TRAMP (TNFR-related apoptosis mediating protein),[213] this molecule appears to be somewhat analogous to TNFRI in that it can activate both NF-?B and induce apoptosis.[209, 213] The receptor has a 24 aa residue signal sequence, a 178 aa residue extracellular region, a 23 aa residue transmembrane segment, and a 192 aa residue cytoplasmic domain.[209, 210] In the extracellular region there are four cysteine-rich motifs.[210] At the aa sequence level, DR3 is approximately 30% identical to TNFRI, and 25% identical to Fas.[210] About a dozen alternate splice forms are known for DR3, many coding for potentially soluble forms.[211-213] The shorter isoforms seem to be expressed by resting cells that subsequently switch to expressing the full-length (413 aa residues) isoform upon activation.[212] Cells identified as expressing DR3 include T and B cells[212] and HUVECs (human umbilical vein endothelial cells). A HUVEC library was used to clone DR3.[209] There is currently no known ligand for DR3.

DR4:

DR4 (or Death Receptor 4) is one of three known receptors for TRAIL.[214] DR4 is a 468 aa residue type I (extracellular N-terminus) transmembrane protein that contains a 23 aa residue signal sequence, a 226 aa residue extracellular region, a 19 aa residue transmembrane segment, and a 220 aa residue cytoplasmic domain. In the extracellular region, there are two cysteine-rich motifs.[214] Although DR4 has a death-domain, it cannot activate NF-kB, and it cannot use FADD, a death domain-associated cytoplasmic protein utilized by Fas, TNFRI and DR3.[214] To date, it is only known to be expressed by activated T cells.[214]

DR5:

DR5 (or Death Receptor 5) is the second of three known receptors for TRAIL.[215] Like DR4, ligation of this receptor can trigger an apoptotic program independent of FADD participation. The molecule is 411 aa residues long, with a very large 51 aa residue signal sequence, a 132 aa residue extracellular region, a 22 aa residue transmembrane segment, and a 206 aa residue cytoplasmic domain. The extracellular region contains two cysteine-rich motifs.[215]

DcR1/TRID:

DcR1 (Decoy Receptor-1)[216] or TRID (TRAIL Receptor without an Intracellular Domain)[215] is exactly what the latter name suggests, *i.e.*, a membrane-bound receptor for TRAIL that possesses no cytoplasmic domain. Found on endothelial cells and lymphocytes, the molecule is 259 aa residues long, possessing a 23 aa residue signal sequence, a 217 aa residue extracellular region, and a 19 aa residue transmembrane domain.[215] There are two cysteine-rich motifs in the extracellular region, which is 50-60% identical at the aa sequence level to the same regions in DR4 and DR5. Without a cytoplasmic segment, this receptor does not signal. Instead, it inhibits responsiveness to TRAIL at the level of the cell membrane.

TR2:

TR2 is a newly discovered, 32 kDa type I transmembrane glycoprotein that has no known ligand at present.[217] Found on T cells, B cells, monocytes and endothelium, the molecule is 283 aa residues long, with a 36 aa residue signal sequence, a 165 aa residue extracellular region, a 23 aa residue transmembrane segment, and a 59 aa residue cytoplasmic domain. The extracellular region contains four cysteine-rich motifs.[217]

GITR:

GITR (glucocorticoid-induced TNFR family-related) is a 228 aa residue transmembrane protein that is suggested to be a close relative of 4-1BB and CD27. Inducible during T cell activation, the molecule has a 19 aa residue signal sequence, a 134 aa residue extracellular region, a 23 aa residue transmembrane segment and a 52 aa residue cytoplasmic domain. It has three cysteine-rich motifs in its extracellular region. Like 4-1BB, ligation interrupts TCR-DC3-induced apoptosis in T cells.[218]

Osteoprotegerin/OPG:

Named because of its ability to protect bone from breakdown (*i.e.*, inhibit osteoclasts), OPG is a 55 kDa, 380 aa residue, naturally secreted member of the TNFRSF.[219] Most similar to TNFRII and CD40, this

"receptor" has no transmembrane segment, and circulates as a disulfide-linked homodimer. The human, mouse and rat proteins are all equal in length, with human and rat having 94% aa sequence identity. It is unknown what type of "ligand" exists for this receptor.

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